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10/619,729	07/15/2003	Emilio J.A. Roldan	3524.015	7038

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EXAMINER	
ISSAC, ROY P	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 11/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/619,729	ROLDAN ET AL.	
	Examiner	Art Unit	
	Roy P. Issac	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-57* is/are pending in the application.

4a) Of the above claim(s) *47-53 and 55-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-46 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a divisional of 09/830,734 (July 27, 2001), now U.S. Patent 6,605,603, which is a 371 of PCT/EP99/08269 (October 29, 1999), which claims priority to Argentina P 98 01 05446 (October 30, 1998).

This communication is in response to applicant's arguments/ remarks/ amendment filed 10/16/2006.

Election/Restrictions

Applicant's election with traverse of the invention of Group I, claims 32-46 and 54, in the reply filed on 8/24/2006 is acknowledged. The traversal is on the ground(s) that both inventions involve the administration of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphonic acid. As indicated in the requirement for restriction dated, 05/15/2006, the inventions I and II are separate and distinct from each other since they have different modes of operation and have different functions. Each method of treatment relates to a separate and distinct area of pharmaceutical technology. Furthermore, the applicant asserts that the search for both inventions will not be unduly burdensome. However this assertion was found unpersuasive. The search for all inventions would place an undue burden on the examiner in view of the diversity of the medical disorders to be treated and the corresponding diversity in the field of search for each.

The restriction requirement between Inventions I-III was deemed proper and is therefore made FINAL.

Claims 47-53 and 55-57 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/16/2006.

Claims 31-46, and 54 will be examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-39 and 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of bone disorders, does not reasonably provide enablement for the prevention of bone disorders or osteopathies as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue

experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The current invention relates to the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid and for the treatment and prevention of osteopathies and bone disorders as well as the maintenance of healthy bone structure.

The relative skill of those in the art:

The relative skill of those in the art is high, with a typical practitioner having obtained a PhD, M.D. or equivalent advanced degree.

The breadth of the claims:

The claims are considered very broad since they encompass the treatment and prevention of a series of osteopathies and bone disorders including Paget's disease, arthritis, peridental osteopenia, adolescent scoliosis, fracture, disuse osteopaenia, post-transplant osteopenia, metabolic bone disease, osteopenia of prematurity and ossification disorder, a group of diseases with very diverse etiology.

The amount of direction or guidance presented and the presence or absence of working examples:

The specification does not provide any examples of the prevention of any diseases.

The predictability or lack thereof in the art: the instant claimed invention is highly *unpredictable* as discussed below:

Prevention of the series of diseases that can be considered osteopathies and bone disorders including, fracture, arthritis, and metabolic bone disease, is not the same as the treatment of a disease condition. In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method, one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?

2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely suppress all symptoms?

3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active

agent accumulate in the subject's tissues? Is the minimum dose necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

For this reason, many of the therapies that are useful for treating a disease are not useful preventing the disease. For example, antibiotics, chemotherapeutics and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer. Thus, it is highly unlikely that any of osteopathies or bone disorders, including arthritis and fracture, can be prevented by the administration of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid of the instant application.

The quantity of experimentation necessary:

In order to determine whether the claimed method can prevent the diverse series of diseases and disorders that can be considered osteopathies and bone disorders, one of ordinary skill in the art will need to answer the questions posed above, which will require significant intellectual and financial input, and an effort that will be collaborative in nature with clinical physicians, organic chemists and biochemists involved, resulting in enormous burden on one of skill in the art to practice the invention as claimed.

Thus, the specification fails to provide clear and convincing evidence in sufficient support for the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid for the prevention of any disease condition as recited in the instant claims.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the ***Wands*** factors as discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in ***undue experimentation*** to practice the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 44-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 44-46 recites "after the administration to the patient – the 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid, or any of its soluble salts or any of its hydrates are present at extracellular concentration in a range of between 10^{-6}M and 10^{-10}M" renders the claim indefinite. It is not clear how much of the 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid needs to be administered to a patient to achieve such extracellular concentration. As such, one of ordinary skill in the art will not be apprised of the metes and bounds of claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32, 35, 41and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Beek et. al. (WO 97/02827; PTO-892, Cited by the examiner).

Beek et. al. discloses the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid for the treatment of all forms of osteoporosis, arthritis and periodontal diseases, as well as diagnostic purposes. (Page 3, last paragraph to Page 4, line 2; Page 5, Paragraph 3). Beek et. al. discloses the use of said compound in combination with calcium salt, vitamin D and parathyroid hormone. (Page 4, Paragraph 2; Claims 5-10, Page 15). Beek et. al. further discloses that 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid is devoid of any antiresorptive activity. (Page 5, Paragraph 3, lines 1-5). 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid is disclosed as useful in the treatment of diseases in which antresorptive action is unwanted. . (Page 5, Paragraph 3, lines 5-10). Since the treatment of all forms of osteoporosis and arthritis and periodontal diseases is required "for maintaining a healthy bone structure", said treatment is considered encompassed by the "method for maintaining a healthy bone structure".

Thus, claims 32, 35, 41 and 54 are deemed anticipated by Beek et. al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 33-34, 36-40 and 42-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Beek et. al. (WO 97/02827; PTO-892, Cited by the examiner) in view of Brumsen et. al. (Reviews in Molecular Medicine, 76(4), 1997, pp266-283, web printout; PTO-892, Cited by the examiner).

The disclosure of Beek et. al. is disclosed above in the 102 rejection. Furthermore, Beek et. al. discloses that in comparison with olpadronate, 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid has similar binding activity (Figure 1) while without the undesired antiresorptive activity. (Figure 7; Page 5, Paragraph 3, lines 1-5).

Beek et. al. does not expressly disclose the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid for administration to healthy patients or patients without osteopathies or to human being at or above the age of 40 years or to a child or for patients who have undergone corticosteroid

treatment or for combating bone disease in a child. Beek et.al does not expressly disclose any extracellular concentraton of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid.

Brumsen et. al. discloses the use of 1-hydroxy-3-(N,N-dimethylamino)-propylidene-1,1-bisophosphonate (olpadronate), a molecule with strong structural similarity to 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid. Note that the only difference between the two compounds is the substitution of the hydroxyl group for the amine group at 1-position. Brumsen et. al discloses that long term olpadronate administration to children severe osteoporosis was devoid of any adverse effect on the growing skeleton. (Web printout; Page 20, Paragraph 2). Brumsen et. al. discloses the use of bisphosphonates for patients who underwent glucocorticoid treatment. (Web printout; Page 21, Paragraph 1). Brumsen et. al further discloses that bisphosphonates are well known for treatment for patients with postmenopausal osteoporosis, a condition generally affecting those above 40 years age.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid to treat children in place of olpadronate because Brumsen et. al. discloses olpadronate for the treatment of children and Beek et. al. discloses 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid to have superior antiresoprtive activity in direct comparison with olpadronate. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat healthy patients, and patients without

osteopathies with 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid because it is devoid of any unwanted antiresorptive activity and beneficial effects. Furthermore, Beek's disclosed use for diagnostic purposes is expected to include healthy individuals as well as individuals without osteopathies.

One of ordinary skill in the art would have been motivated to use 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid to treat children as well as adults because olpadronate is well known for such treatments and a direct comparison of olpadronate with the compound of the instant application by Beek et. al. disclosed that the compound of the instant application is devoid of antiresorptive activity.

One of ordinary skill in the art would have reasonably expected that the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid as claimed herein would be successful because Beek et.al. showed in comparison with olpadronate, the compound of the instant application has similar or better effects.

Thus the invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

11/27/06

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